In the Specification:

Please amend the specification as follows:

Please replace the paragraph beginning on page 1, line 22 with the following amended paragraph:

--Triple quadrupole instruments are the most common MS-MS instruments. A continuous ion source, ~~like~~ e.g., electrospray (ESI), introduces ions into a first quadrupole mass filter, which is tuned, such that only ions of interest pass the mass filter. The rest of the primary beam components are rejected and lost. Selected ions are transmitted into a so-called "collision induced dissociation" (CID) cell, filled with gas at pressures of few tens of millitorrs and equipped with a radio frequency (RF) quadrupole guide. The kinetic energy of the injected ions is controlled by an electrostatic bias on the mass filter and is adjusted to induce ion fragmentation via gas collisions. Fragment ions are collisional dampened in a CID cell and then introduced into a second quadrupole for mass analysis. Since mass scanning in a second quadrupole takes time and causes additional ion losses by factor of c.a. 1000, triple quadrupole instruments are mostly used for detection of known species with known masses of parent and fragment ions.--

Please replace the paragraph beginning on page 2, line 1 with the following amended paragraph:

--The introduction of ~~quadrupole-time-of-flight~~ quadrupole time-of-flight tandem mass spectrometers (Q-TOF) strongly enhanced throughput of MS-MS instruments (see Morris et al., Rap. Comm. Mass. Spectrom., v.10, pp. 889-896, 1996). The triple quadrupole was modified, such that the second quadrupole mass filter was replaced by an orthogonal TOF MS (oa-TOFMS). This substitution gave an advantage of parallel analysis of all fragment ions at once and, hence, higher sensitivity and faster acquisition in a second MS, as well as enhanced resolution and mass accuracy of a second MS. However, the quadrupole is still used for parent ion selection, accompanied by rejection of all ion species but one. The idea of parallel analysis has not been extended ~~onto~~ to parent ions.--

Please replace the paragraph beginning on page 2, line 10 with the following amended paragraph:

--Another common MS-MS device is a Paul ion trap mass spectrometer (ITMS), well described in March, R.E., Hughes R.J. Quadrupole storage mass spectrometry, Willey-Interscience, New York 1989. Ions, produced in the ion source, are periodically injected into an ITMS and are trapped within the ITMS by a ~~radio frequency~~ radio frequency (RF) field. ~~Unwanted~~"Unwanted" species are removed ~~by~~, e.g., by applying a broadband resonant AC signal, so that only ~~ions of interest~~ ions of interest remain in the trap. Selected parent ions are then excited by a separate AC field, resonant with the secular motion of the precursor. Parent ions gain kinetic energy and fragment in energetic collisions with a buffer gas. Fragments are mass analyzed using a resonant ejection technique. The amplitude of an RF field is ramped such that ions leave the trap sequentially according to their m/z values.--

Please replace the paragraph beginning on page 2, line 20 with the following amended paragraph:

--It also has been known to couple a 3-D Paul trap with a TOF analyzer for more accurate mass analysis of fragment ions. See Quin and D. Lubman, Rap. Comm. Mass. Spectrom., 10, 1079, 1996 and WO ~~0~~99/39368 by Shimadzu. A linear ion trap (LIT) has been coupled to a TOF analyzer in U.S. Patent No. 5,847,386 by ~~D. Douglas~~Thomson et al., ~~in~~ U.S. Patent No. 6,111,250 by B.A. Thomson and L.L. Joliffe, ~~in~~ U.S. Patent No. 6,020,586 by T. Dresch et al. and ~~in~~ WO 01/15201 by B. Reinhold and A. Verentchikov. All ion trap tandems are mostly oriented on multiple stage MS-MS analysis. Parent ions are selected with a loss of other ion components.--

Please replace the paragraph beginning on page 2, line 28 with the following amended paragraph:

--Recently introduced tandem time-of-flight mass spectrometers (TOF-TOF) are the closest prototypes to the below described invention by similarity of employed hardware. Examples of TOF-TOF are described in U.S. Patent No. 5,032,722 by Schlag et al., U.S. Patent No. 5,464,985 by T.J. Kornish et al., U.S. Patent No. 5,854,485 by T. Bergmann, ~~in~~ WO 99/40610 by M.L. Vestal, ~~in~~ U.S. Patent No. 6,300,627 by C. Koster et al. and ~~in~~ WO 99/01889 by C. Hop. In all TOF-TOF tandems, a pulsed ion beam is time separated in a first, high-energy TOF and filtered by timed ion selector, so that only ~~ions of interest~~ ions of interest pass into the CID cell. The CID cell is filled with gas at a low gas pressure (usually below lmtorr) to induce single high-energy collisions with the buffer gas sufficient for ion fragmentation, but still retaining short duration to maintain an ion packet. A pulsed beam of fragment ions is analyzed in a second, high energy TOF. To handle the large energy spread of the fragment ions, the second TOF employs either quadratic field potential or an additional pulsed acceleration.--

Please replace the paragraph beginning on page 5, line 19 with the following amended paragraph:

--Two of those novel TOFl analyzers employ a combination of a confining radio frequency (RF) field with a DC quadratic field, providing temporal focusing of the ion beam with a relatively large energy spread. Those analyzers are capable of operating at a particularly low ion energy ranging from 1 to 10 eV. In one preferred embodiment, the novel TOFl analyzer comprises a linear multipole ion guide, preferably quadrupole, surrounded by DC mirrors. DC mirrors on both ends are turned on and off to provide ion injection from one TOFl end, and multiple ion reflections and subsequent ion release from another end. In another preferred embodiment, the novel TOFl analyzer comprises two external rows of DC electrodes and two internal rows of RF-only rods, oriented across TOFl axis. The structure forms a two-dimensional ~~RF-tunnel~~RF tunnel combined with quadratic potential distribution along the TOF axis. Ions are injected into the TOFl at a small angle to the axis, experience multiple reflections along the axis, slowly shift across the axis and leave TOFl after several reflections.--

Please replace the paragraph beginning on page 5, line 32 with the following amended paragraph:

--Another three novel analyzers are electrostatic devices, operating at medium energy around 100-300 eV. One of them, a ~~'spiratron'~~ "spiratron," comprises a pair of coaxial cylindrical electrodes with DC voltage applied between them. Ions are injected between the electrodes at a small angle to their axis. Medium energy (100 eV) ions turn around central electrodes while drifting slowly along the axis. After a number of turns, ions leave TOF1 through a cut-off boundary, which is formed by a double-sided printed circuit board to avoid DC field disturbance. Other two electrostatic separators are planar and cylindrical multi-pass analyzers, employing gridless mirrors, simultaneously acting like a lens. The effective flight path is extended by use of a multi-pass mode, so that a 10ms time scale is achieved despite a higher energy (compared to RF assisted TOF1).--

Please replace the paragraph beginning on page 6, line 23 with the following amended paragraph:

--The TOF-TOF tandem of the invention is expected to separate parent ions at a moderate resolution, mostly limited by speed of the second TOF MS, e.g., 10μs. The estimated resolution of TOF1 on the order of 300 (see detailed description) is still sufficient to isolate a group of isotopes of parent ions and is much higher than the resolution of parent separation in the prior art ion mobility spectrometer. Higher resolution of separation could be achieved in longer TOF1 or by periodic selection of ions by a time gate in front of the CID cell.--

Please replace the paragraph beginning on page 6, line 30 with the following amended paragraph:

--The invention permits multiple strategies for data acquisition. In a simple~~st~~ and robust approach, MS-MS data are acquired continuously and MS-MS spectra of multiple parent ions are reconstructed afterwards. It is wiser, though, to perform MS-MS analysis in two stages. At first, MS-only stage, parent ions are continuously admitted into the TOF2 for mass analysis of parent

ions. Information on masses of parent ions is used for a second MS-MS stage. The time gate opens only at a time of arrival of multiple parents of interest to improve the resolution of parent ion separation and to avoid signals from chemical background. The TOF2 signal is also acquired for selected time windows only to reject meaningless data flow. Similar information on parent ions may be obtained using an optional on-line detector located anywhere after TOFl. This information could be also used for subsequent computer deconvolution of overlapping temporal profiles of adjacent fragment families (similar to methods generally employed in chromatography and chromatography/mass spectrometry).--

Please replace the paragraph beginning on page 8, line 19 with the following amended paragraph:

--A method of tandem mass spectrometry analysis of the invention comprises the steps of: generating an ion pulse in an ion source, containing a mixture of different analyte ions; separating the analyte ions according to ~~time-of-flight~~ time of flight within a first time-of-flight mass spectrometer, and, thus, generating a train of ion packets in a sequence of their masses; sequentially fragmenting the analyte ions without mixing the separated ion packets; rapidly mass analyzing the fragmented ions within a second time-of-flight mass spectrometer at a time scale much shorter, than a time scale of the first separation step; acquiring fragment mass spectra for multiple analyte ion mass-to-charge ratios at a single ion pulse out of the ion source; and, optionally, summing the fragment spectra for each of the analyte ions over multiple source pulses.--

Please replace the paragraph beginning on page 9, line 3 with the following amended paragraph:

--Referring to Fig. 1, the method is illustrated by a block diagram of the major tandem MS-MS components. The generic TOF-TOF instrument with time-nested acquisition 11 comprises a sequentially communicating pulsed ion source 12, a first time- of-flight mass spectrometer ~~TOFl 13~~ TOF1 13, a fragmentation cell ~~CID/SID 14~~ CID/SID 14, a second time-of-flight mass spectrometer TOF2 15 and a data system 16 for time-nested acquisition. The

pulsed ion source is biased compared to the TOFl spectrometer at a small potential difference by voltage supply 17, and the TOFl is biased compared to the CID cell at a potential difference by voltage supply 18. An optional timed gate 19 may be inserted between the TOFl 13 and the CID cell 14 to enhance TOFl separation.--

Please replace the paragraph beginning on page 9, line 12 with the following amended paragraph:

--Briefly, in operation, the pulsed ion source generates an ion pulse of analyte (parent) ions and injects ions into the TOFl at a reduced energy, typically between 1 to +300 eV, controlled by a voltage supply 17. This is an important difference between the current invention and the prior art, since TOF spectrometers are usually operated at energies between 3 and 30keV. Another important difference is the concomitant extension of the flight length of TOFl, preferably up to lengths of 5-50 m, depending on the ion energy and flight time required. Separation in TOFl occurs typically in several milliseconds. As a guiding example, let us consider the effective length of TOFl L1=8m, mean ions energy E=3 eV and ion mass m=1000 a.m.u. In this example, ion velocity is V=800 m/s and the flight time is 10ms. The same ~~time-of-flight~~ time of flight could be provided by a system with an effective flight length L1=45 m and mean ion energy E1=100 eV. Time-separated parent ions are sequentially ejected out of TOFl into the CID cell at an energy level controlled by a DC bias between TOFl and the cell. Energetic collisions with the carrier gas molecules convert the parent ions into fragments. Subsequent gas collisions cause collisional dampening of fragment ions. Fragments rapidly travel through the cell and are injected into the TOF2 spectrometer. TOF2 separates fragment ions at a much shorter time scale, between 10 and 100μs. This could be provided by a system with effective path length of L2=1 m and mean energy E2=5-10 keV. Drastic difference in time scales of TOFl and TOF2 allows data acquisition of multiple fragment spectra, corresponding to different parent ions between source pulses. The specialized data acquisition system 16 acquires multiple fragment spectra in a time-nested fashion, where individual spectra are not mixed together. Fragment spectra for each parent ion are integrated over a number of ion source pulses.

Thus, ion pulse, generated in the ion source, is used for acquiring a full set of MS-MS data for multiple parents without rejecting ions at all stages.--

Please replace the paragraph beginning on page 10, line 22 with the following amended paragraph:

--In another operation mode, which should be called ~~'data dependent acquisition',~~ "data dependent acquisition," MS-MS analysis occurs in two steps. ~~On~~ In the first step, mass spectrum of parents is acquired in a TOF2, while TOFl and CID cell pass ions continuously without fragmentation. In some embodiments it is possible to by-pass TOFl altogether to avoid ion losses and accelerate analysis. On the second step, the instrument is operated as MS-MS, i.e., the TOFl separates parent ions, the fragmentation cell forms fragments, and the TOF2 acquires fragment mass spectra in the time-nested data fashion. The time-nested acquisition is enhanced by utilizing the information on the parent ion masses and avoiding data acquisition at blank times, when no parents are coming. An optional timed gate 19 may be used to enhance TOFl separation as well as suppression of chemical noise. It is naturally expected, that ion packets coming out of TOF1 are shorter, than the same ion packet at the exit of the CID cell. The timed gate admits ions only at multiple narrow time windows, corresponding to arrival of parent ions. Such gating suppresses ion signals coming from chemical backgrounds and improves detection limit. Gate operation may also be used to enhance separation of a pair of parent ions of close mass by sacrificing sensitivity. Several sets of MS-~~Ms~~MS data are acquired, while timed gate admits only one parent mass of a pair at a time.--

Please replace the paragraph beginning on page 11, line 6 with the following amended paragraph:

--Having described the general method for the purpose of clarity, the detailed embodiments will be first discussed on the level of individual components and only then presented as examples of integrated TOF-TOF apparatus. Though some employed components are well known in the art, their configurations and parameters are altered to suit purposes of the

invention. To understand selected compromises, let us first look at major challenges in TOF-TOF method and apparatus.--

Please replace the paragraph beginning on page 11, line 12 with the following amended paragraph:

--The method of the invention is highly counterintuitive, since it would be referred to as undoable for multiple reasons. One of ordinary skill in the art would contend that: TOF1 resolution would be extremely low, since ion energy spread in the source is comparable to ion energy in the TOF1; TOF1 resolution would also suffer because of a large turn around time (time spread, caused by initial velocity spread) in a weak accelerating field; ion losses through the TOF1 are expected to be devastating, because of expected large length of TOF1, and because of high divergence of slow ion beam in the TOF1, ion losses are expected to be even higher, since vacuum stage of TOF1 and ~~gas~~ the gas-filled CID cell should be separated by a small aperture; and it also looks unlikely to have quick transmission through the CID cell in the time scale of 10 to 100μs. Most existing CID cells have time spreads on the order of 200 to 10,000μs. None of the available commercial data acquisition systems currently employed in TOF technology is capable of handling expected data flow rate.--

Please replace the paragraph beginning on page 12, line 13 with the following amended paragraph:

--In operation, the RF field provides a radial confinement, shown by arrows 37 on Fig. 3. Radial RF confinement does not affect ion motion along the axis. An Aaxial 15 parabolic electric field is formed by field penetration between multipole rods. The parabolic field provides ion axial reflections with a period, grossly independent on ion energy and proportional to the square root of ion m/z. Pulsing potentials on the mirror ends allows switching between ion injection into TOF1, ion reflections 39 within TOF1 and subsequent ion release on the other end of TOF1. The effective flight path $L1_{EFF}$ is approximately $N\pi+1$ times higher than TOF1 length L, where N is a number of full turns. Overall, RF confinement and multiple reflections allow prolonged time

separation without ion losses, while quadratic potential enhances TOFl resolution and allows separation of a slow ion beam with a high relative energy spread.--

Please replace the paragraph beginning on page 12, line 24 with the following amended paragraph:

--The ideal quadratic scheme is altered by the presence of a free flight segment on the way in and the way out of TOFl. According to the above-cited publication by Makarov et al., even in the case of substantial field free flight, here c.a. 30% of L_{EFF}, a mass resolution of 2000 is achievable for ion pulses with relative energy spread up to 50%. To keep free flight path below $0.3L_{EFF}$, the scheme requires at least 5 reflections, corresponding to 2 full turns. It helps to increase $L1_{EFF}$ to $7.3L_z$ but reduces mass range of parent ions to a factor of two, i.e., $M_{MAX}/M_{MIN} \leq 2$.--

Please replace the paragraph beginning on page 13, line 4 with the following amended paragraph:

--In operation, rods 46 with alternating RF potential form an RF tunnel, confining ions in the Z direction. The potential on electrodes 43, 44 is distributed by a resistor chain to form a quadratic potential along the X-axis with the minimum at the center plane of TOF. The field of external DC electrodes penetrates into the RF channel, providing a weaker but still quadratic potential distribution. Not accounting for fringing fields, there is no field in the Y direction. Ions are injected at a small angle to the X-axis and are deflected by deflection plates 45 to double the deflection angle for ions with mean energy. The deflection reduces Y-spatial spread, caused by X-energy spread. Ion motion is a combined slow drift along the Y direction and of multiple reflections along the X direction. Overall, ion trajectories have a wave shape, ending at the boundary of the RF tunnel. Ions gain some spatial spread at the exit of TOF, which is partially compensated by ion post-acceleration and focusing by a lens.--

Please replace the paragraph beginning on page 13, line 32 with the following amended paragraph:

--In both of the described TOF mass separators, the period of each reflection is grossly independent of ion energy and is proportional to the square root of the ion m/z. Ions are confined by the RF field, and ion losses are practically eliminated. Introduction of the novel low-energy TOF analyzers makes the present invention practical, resolving the above-mentioned objections: a) The high relative energy spread is compensated by quadratic distribution of potential in the ion mirror, created by a DC electric field penetration into multipole guide or tunnel; b) Because of the TOFl ability to operate at a high relative energy spread, it can operate at a much lower ion energy and at a much longer time scale, compared to conventional TOF, and, ~~, As~~ a result, the apparatus tolerates a much longer ion pulse out of the ion source, and turn around time is no longer an obstacle; c) Drastic difference in time scales of TOFl and TOF2 allows time-nested data acquisition; d) Ion losses are practically avoided by guiding ions within the radio- frequency guide or tunnel; e) Ion confinement by the RF field and ion post-acceleration ~~is front~~in front ~~-~~of the CID cell allow full transmission of the ion beam into the CID cell; f) Time spread in the CID cell is reduced by using a short, high pressure cell with an additional axial DC field~~;~~, and g) A ~~T~~transient recorder with a large and fast averaging memory has been recently introduced by Swiss company Acquiris (www.acquiris.com).--

Please replace the paragraph beginning on page 14, line 24 with the following amended paragraph:

--In operation, samples for analysis are prepared within matrices known in the art, and deposited on the sample plate 53. The pulsed laser 55 illuminates the sample and generates a short pulse of analyte ions. Ions are known to be ejected with a 300 to 600m/s velocity, which corresponds to initial ion energy between .5 and 1.5 eV for 1kD ion. The ions are accelerated by a few ~~Volts~~ volts potential bias. One can estimate that 1kD of ions leave the ion source with few microseconds time spread and less than 1 eV energy spread. The major drawback of a vacuum MALDI ion source is ion temporal instability, well described in conventional, high energy MALDI. The invention is likely to be applicable to softer MALDI ion sources, employing soft

matrices or an ~~infra-red~~infrared laser. Temporal stability of ions is improved by the collisional cooling, described below.--

Please replace the paragraph beginning on page 15, line 31 with the following amended paragraph:

--In operation, the quadrupole is filled with buffer gas at 1 to 100mtorr pressure. Differential pumping system 75 reduces gas load on TOFl pumping. Ions are generated in the ion source 72 and continuously fill the RF-only quadrupole ion guide 74. Gas collisions dampen ion kinetic energy and confine ions along the quadrupole axis and at the bottom of a DC well created by electrodes 76 and aperture 77. Periodically, a potential on electrodes 76 and exit aperture 77 ~~are~~ is adjusted to eject the stored ions in the axial direction into TOFI. This construction produces an ion pulse having less than 1-5 eV energy spread and less than 10-50μs time spread.--

Please replace the paragraph beginning on page 16, line 14 with the following amended paragraph:

--Referring to Fig. 8, the TOF-TOF method employs a short, high gas pressure CID cell 81 for ion fragmentation. The CID cell 81 comprises a vacuum housing 82, an entrance lens 83, a CID chamber 84 connected to a gas inlet 85, an RF focusing device 86 with optional DC electrodes 87, enclosed in the CID chamber, and exit ion lens 88. The CID cell also comprises an optional timed ion selection gate 89. The gas inlet feeds buffer gas into CID chamber. The CID chamber 83 comprises apertures 83A, B. The vacuum housing 82 comprises apertures 82A, B, and vacuum pump 82C. The RF focusing device is preferably ~~a~~ an RF-only quadrupole.--

Please replace the paragraph beginning on page 17, line 31 with the following amended paragraph:

--In operation, ion packets of time-separated parent ions are pulse accelerated to c.a. 50 eV/kDa specific energy, being bunched by a lens 92. Bunching, previously employed in magnet sector-TOF tandems, is known to compress ion packet duration below $dT<1\mu s$. The lens 92

focuses and steers parent ion packet 99 onto the center of the probe 93. The ion beam impinges the surface at some angle, ~~say for example,~~ 45 degrees. Medium energy collisions with a fluorocarbon mono-layer surface are known to induce fragmentation of peptides and small molecular ions. Fragment ions bounce off the surface with c.a. 500 to 2000 m/s velocity, traveling less than 2mm within dT≤1μs of primary ion packet duration. During impinging, a small retarding potential is applied to the mesh 97, preventing leakage of fragment ions into the TOF2 analyzer. After an appropriate delay, corresponding to impinging of the entire primary ion packet, pulse generators 94 and 98 are triggered, and electric pulses are applied to the probe 93 and the mesh 97. Fragment ions are pulse accelerated into the TOF2 analyzer.--

Please replace the paragraph beginning on page 18, line 25 with the following amended paragraph:

Operation of o-TOF is well described in the art. A continuous or pulsed ion beam, accelerated to c.a. 10 eV, enters the acceleration region. Periodic pulses accelerate the ions orthogonal to c.a. 3keV and inject them into the TOF analyzer. Ions get reflected in the ion mirror and hit the TOF detector 105. A portion of initial ion beam is acquired on the in-line detector 106. To accommodate rapid analysis of fragment ions, parameters of the o-TOF are slightly altered. The analyzer is small - L=10 to 20cm, and operates at high TOE energy (5 to 15kV) to accommodate high repetition rate, c.a. 100KHz. A small size analyzer allows operation at a gas pressure slightly below 1E-5torr. The conventional TOF analyzer is also modified by using a high current secondary electron multiplier (SEM) or hybrid MCP/PEM ~~for as a~~ detector and by using a fast averaging transient recorder for data acquisition system. Small length and short flight time pose a limit on TOF2 resolution. To improve resolution of TOF2, one can increase the flight time in TOF2, while limiting the time windows of admitted ions by one of: 10μs time gate interleaved between IMS scans and use slower pulse rate of TOF2; pulse TOF2 at lOOKHz rate and divert ions within TOF2 onto several detectors; or pulse TOF2 at lOOKHz rate and use a position sensitive detector in TOF2. TOF2 is optionally equipped with an in-line detector in order to avoid acquiring a signal in blank time, when no ions are coming from TOFl .

Please replace the paragraph beginning on page 19, line 15 with the following amended paragraph:

--In operation, a pulse of fragment ions is accelerated within the SID cell 91, flies through the field free region 112, ~~are~~ is reflected in the ion mirror 115 and hits the detector 114. Ion trajectories are shown by lines 119. The signal from the detector is acquired on the transient recorder 118. Again, for the purposes of rapid data acquisition, the analyzer is relatively short, L=10 to 20cm, and operates at high acceleration potential to accommodate a high repetition rate of 100KHz.--

Please replace the paragraph beginning on page 19, line 21 with the following amended paragraph:

--Having described individual components, it becomes easier to grasp the concept and peculiarities of the integrated TOF-TOF method and apparatus. Below ~~find~~ are specific examples of TOF-TOF tandems of the invention, though not limiting a multiplicity of viable combinations.--

Please replace the paragraph beginning on page 20, line 1 with the following amended paragraph:

--In operation, continuous ion source 71 feeds parent ions into the storage quadrupole 74. Once every 10 to 20ms, ions are ejected from the storage quadrupole by pulsing potentials on DC electrodes 76 and exit aperture 77. An ejected ion packet containing a multiplicity of different parent ions is less than 10μs long and has less than 1 eV energy spread. Mean energy of the ejected ion pulse is adjusted to c.a. 2 eV by selecting pulse potentials on electrodes 76 and 77. Ions are admitted into the TOFl separator by dropping the potential of the first mirror 33A. Ions are radially trapped by the quadrupole RF field, but are free to travel along the quadrupole axis. Once parent ions of all masses (limited to the ratio Mmax/Mmin=2) pass the first mirror, the first mirror 33A is turned on. The second mirror 33B has been turned on within the previous cycle. The ions experience multiple reflections, preferably 5 reflections, between the two mirrors with quadratic potential distribution along the TOFl axis. The period of oscillation is grossly

independent on ion energy and is proportional to the square root of parent ion mass. The effective flight path of the analyzer is up to $2\pi+l\alpha=7.3$ times longer than the physical length of TOF1. After the preferred numbers of reflections, ions are released out of TOFl by lowering the potential of the second mirror 33B. The train of time-separated ~~ion-packets~~ion packets enters the CID cell. A typical time scale of time separation is on the order of l0ms, measured as a flight time of lkDa ions, and the duration of each packet, corresponding to parent ion mass, is approximately 10μs. Parent ions are separated with c.a. 1000 time resolution, corresponding to 500 mass resolution.--

Please replace the paragraph beginning on page 20, line 21 with the following amended paragraph:

--After leaving TOFl, each ion packet is accelerated to a specific energy of 50 eV/kDa, sufficient to induce fragmentation in gas collisions. Ions are focused by a lens system and injected into a high pressure CID cell via aperture 82A and 84A. The ions fragment in the cell, and fragment ions are collision-dampened and confined by an RF field. The cell is actively emptied by pulsed potential of two CID apertures 84A, B, synchronous and time shifted relative to TOF2 pulses. Ions enter orthogonal acceleration region 102, get injected into TOF2 analyzer, being time separated and, thus, mass analyzed in TOF2. Synchronized injection into TOF2 eliminates time gaps, i.e., almost no fragments are lost between TOF2 pulses. Synchronous injection also improves the duty cycle of TOF2. Most of the fragment ions are contained within the acceleration region 102 at the time of TOF2 pulse. --

Please replace the paragraph beginning on page 21, line 3 with the following amended paragraph:

--In the above-described apparatus there are three almost equal (c.a.l0μs) sources of time-spread, deteriorating resolution of TOFl separation: time-spread gained in the ion source; and time-spread in the CID cell and due to TOF2 digitization (i.e., acquiring spectra at discrete time). Assuming no correlation between those three sources, the overall time spread is estimated as 17μs (square root of three higher than each spread). The resulting resolution of TOFl

separation becomes equal to 300, which is still considered to be a fair resolution for parent-ion separation. For comparison, TOF1 resolution in commercial MALDI TOF-TOF is c.a. 100, and quadrupole resolution in Q-TOF in a high sensitive mode is c.a. 300. Resolution of TOF1 of the present invention can be potentially improved by one of the following means: increasing the length of TOF1 above 1m; optimizing ion energy within TOF1; applying a timed gate with multiple narrow mass windows, interleaved between scans; pulsing TOF2 faster and diverting ions onto several detectors; and using a position sensitive detector in TOF2.--

Please replace the paragraph beginning on page 21, line 29 with the following amended paragraph:

--In operation, laser 65 pulses produce a short burst of primary ions off the sample plate 63 at a repetition rate of 50 to 100Hz. The source chamber 62 is filled with gas to relax ion internal energy and prevent ion decomposition. Ions are sampled through a thin gas layer by electric field and gas flow, so that each ion packet remains shorter than 10μs and has an energy spread less than 1 eV. The ion packet is accelerated into the multi-reflecting TOF1 41 at a small angle to the Y axis by another few ~~Volts~~ volts of potential provided by low voltage bias supply 66. The steering plates 45 double the angle to reduce spatial spread in the X direction, related to the Y axis energy spread. Ion motion within TOF1 has three independent components - oscillation in confining RF field in Z-5 direction, multiple reflections along the Y axis with a period almost independent on ion energy, and a slow drift along the orthogonal -X axis. After several Y bounces, the ions leave TOF1 and enter the bunching lens 92 of the SID cell 91, being time separated into a train of ion packets and aligned according to their m/z ratio. Multiple reflections at a small ion-energy allow prolonged time separation in the order of 10ms. Since a quadratic DC field in TOF1 compensates for ion energy spread, separation in TOF1 does not increase the 10μs time spread of ion packets. Thus, after leaving TOF1, the parent ions are separated with a c.a. 300 to 500 mass resolution.--

Please replace the paragraph beginning on page 22, line 13 with the following amended paragraph:

--Periodically, ~~say~~ for instance, once in every 10μs, ions are time bunched into c.a. lμs packets and spatially focused to c.a. lmm by a pulsed lens 92. Pulse-focused ~~ion packets~~ion packets hit the surface of the SID probe 93 coated with a fluorocarbon mono-layer. Collisions with the surface induce ion fragmentation. Fragments, slowly moving from the surface, are spread for c.a. lmm within lμs time. A delayed electric pulse applied to the probe 93 accelerates the fragment ions and injects them into the second TOF2 111 analyzer. Initial parameters (i.e., parameters prior to the probe pulse) of fragment ions are good enough to carry mass analysis in TOF2 with the resolution of a couple thousand. A signal is detected on the SEM 114 with high dynamic range. A Ssignal is passed to the transient recorder 113, and data are acquired in a time-nested fashion. TOF2 transients, representing fragment spectra of various parent ions, are not mixed together. Each fragment mass spectrum obtains a time tag of TOFl separation, measured as a time between source pulse and bunching lens pulse. TOFl time tags carry information on parent ion m/z ratio. TOF2 spectra with the same TOFl time tag are averaged over multiple laser pulses to improve signal to noise ratio.--

Please replace the paragraph beginning on page 23, line 1 with the following amended paragraph:

--Referring to Fig. 14, another embodiment of a low-energy, time-of-flight separator 121 comprises an electrostatic lens 122, a deflector 123 and an analyzer, consisting of an entrance unit 124, two coaxial electrodes 125 and 126 with DC voltage applied between them, and exit unit 127, followed by deflector 128 and lens 129. The described device is known as a "spiratron" and is described in: Bakker ~~J.M.B.~~ J.M.B., The Spiratron, In: *Adv. In Mass Spectrom.*, London, 1971, v.5, pp. 278-280. The novelty is introduced by using the device as a low energy separator in a tandem TOF system.--

Please replace the paragraph beginning on page 23, line 8 with the following amended paragraph:

--In operation, an ion beam from a pulsed ion source 71 is transformed by a lens 122 into a much wider beam with proportionally lower angular spread (a "quasi-parallel beam"). This beam is deflected by the deflector 123 to provide a controlled angle of inclination α relative to the axis of the electrodes 125 and 126. The same effect may be achieved, for example, by positioning electrodes 125 and 126 at a fixed angle. The ion beam would enter the electrostatic radial field between electrodes 125 and 126 via an aperture in the entrance unit 124. One preferred embodiment of the entrance unit 124 includes 3 double-sided printed ~~circuit~~ circuit boards (PCB). Outside surfaces of these boards would face deflector 123 and have metallization on them to create an equipotential surface. The opposite surfaces of these boards would face the gap between electrodes 125 and 126 and contain a set of metallization strips. These strips are connected to a resistive voltage divider that provides a voltage distribution matching the ideal logarithmic voltage distribution between electrodes 125 and 126 and thus minimizing perturbation of this field along ion trajectories. Exit unit 127 may have a similar construction.--

Please replace the paragraph beginning on page 24, line 14 with the following amended paragraph:

--The novel static TOF1 can be coupled to any of the above-described fragmentation systems and TOF2 spectrometers or fragment analysis. Referring to Fig. 14, TOF1 121 is coupled to the CID cell 81 and the orthogonal TOF 101. The major challenge in this combination is to focus the primary beam onto the entrance of the CID cell. Though the ion beam has a high 100 eV energy and the beam gets wider at the exit, the beam is grossly parallel and can be well focused onto a small aperture by a conventional lens.--

Please replace the paragraph beginning on page 25, line 9 with the following amended paragraph:

--Electrostatic mirrors are designed similar to the mirror in gridless TOF devices. Electrostatic potentials, applied to the mirror electrodes, are tuned to satisfy conditions of spatial

focusing and time-of-flight focusing. Graph 160 shows the type of axial potential distribution U(x), satisfying those requirements. To provide spatial focusing along the Z direction, each of the electrostatic mirrors 153 forms a lens with a focal point, located near the center plane of the free flight region (shown by a dashed line). The ion beam (line 159), starts as a parallel beam at the entrance window 156. After the first reflection in the right side mirror, the beam is focused into a point at the middle plane. Note, ~~that~~ focusing of all ions is presented on the drawing by a single ion trajectory, intersecting the axis. After reflection in the left hand mirror, the beam is again converted into a parallel beam.--

Please replace the paragraph beginning on page 25, line 28 with the following amended paragraph:

--According to the inventor's ion optics simulation using the SIMION program, the spatial focusing in the specific TOFl 151 is compatible with time-of-flight focusing in at least the first order, i.e., the first derivatives of flight time on the initial energy and on the orthogonal displacement are equal to zero. The ion beam remains confined ~~if~~ only if initial spatial spread is under 5% of TOFl width and angular spread is below 2 degrees. For energy spread under 3%, the time of flight resolution of TOFl exceeds 10,000. Such initial conditions are realistic for an ion beam accelerated to approximately ≥30 eV after pulse ejection out of linear storing quadrupole.--

Please replace the paragraph beginning on page 26, line 3 with the following amended paragraph:

--Operation at a relatively higher energy (30 to 100 eV), compared to other embodiments, requires a longer ion path in TOFl (30 to 100m) to achieve a millisecond time scale separation in TOF1. The ion path could be easily extended because of the low complexity of TOFl design and its static operation. An instrument of lm length with ~~an~~ approximately 20 full ion turns corresponds to at least a 50m effective flight path.--

Please replace the paragraph beginning on page 26, line 8 with the following amended paragraph:

--Another embodiment of the invention with an "electrostatic multi-pass separator" uses the volume of the separator 151 twice. This is achieved by reverting the Y-component of ion velocity by deflector 158 positioned at the far end of separator 151. The dimensions of deflector 158 are chosen large enough to accept the entire ion beam with account of additional expansion in the Y- direction on the way through separator 151. In this scheme, both deflection of ion trajectory 159 into the separator 151 and its deflection back onto the straight pass to collision cell 81 could be performed by the same deflector 158. Switching off of this deflector allows ~~to bypass~~ bypassing separator 151 altogether, which may be used for parent ion scan in MS-only mode.--

Please replace the paragraph beginning on page 26, line 28 with the following amended paragraph:

--In operation, the cylindrical separator is very similar to the above-described two-dimensional electrostatic multi-pass separator. Ions are forced to make multiple bounces between mirrors, while being spatially focused by lens electrodes. In order to retain ions near the same radius of orbit, an additional potential is applied between the external and internal cylinders 162 and 163. A radial deflecting potential could be also applied between the external and internal cylinders of electrodes 164 and 165.--

Please replace the paragraph beginning on page 27, line 1 with the following amended paragraph:

--The entrance and exit of ions can be organized in multiple ways. Fig. ~~17~~ 16 shows an example of ion introduction through a slit-shaped window 166B with subsequent horizontal deflection, aligning ion beam along the X-axis. To reduce fringing fields, the deflector 170B is surrounded by mesh. Fig. ~~17~~ 16 also shows an example of ion introduction along the X-axis through a segment cut-out in the entire cylindrical analyzer. A b~~B~~eam is injected into the analyzer after horizontal deflection by plates 170C. Field distortion is minimized by using

double-sided PCB, equi-potential within cut-out and with distributed potentials on the side oriented towards cylindrical analyzer. The above-described electrostatic multi-pass separators are suggested for use in comprehensive tandem TOF spectrometer of the invention in a variety of combinations with earlier described pulsed ion sources, fragmentation cell and fast TOF2.--

Please replace the paragraph beginning on page 27, line 23 with the following amended paragraph:

--It should be noted that schemes of Fig. 12, 15, and 16, allow the avoidance of multiple reflections altogether and pass ions to the CIF cell directly. This improves sensitivity and acceleration of the parent ion scan. --